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| 10/665,516 | 09/22/2003 | Andre Stamm | 31672-224618 | 5829 |

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| EXAMINER | |
|---|---|
| SHEIKH, HUMERA N | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/665,516 | STAMM ET AL. | |
| | Examiner | Art Unit | |
| | Humera N. Sheikh | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) ~~OR THIRTY (30) DAYS~~, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### Status of the Application

Receipt of the Request for Continued Examination (RCE) under 37 CFR 1.114 and Applicant's Arguments/Remarks, all filed 10/19/07 is acknowledged.

Applicant has overcome the following rejection(s) by virtue of persuasive remarks: (1) The 35 U.S.C. §103(a) rejection of claims 1-61 over Curtet (USPN 4,895,726) in view of Duclos (USPN 5,776,495) has been withdrawn; (2) The 35 U.S.C. 103(a) rejection of claims 1-61 over Curtet (USPN 4,895,726) in view of Ikeda (USPN 5,952,356) has been withdrawn.

Claims 1-61 are pending in this action. No amendments to the claims have been made herein. Claims 1-61 are rejected.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/19/07 has been entered.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

**Claims 1-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lacy *et al.* (hereinafter "Lacy") (U.S. Pat. No. 5,645,856) in view of Curtet *et al.* (hereinafter "Curtet") (U.S. Pat. No. 4, 895,726).**

The instant invention is drawn to a suspension of micronized fenofibrate in a solution of at least one hydrophilic polymer, wherein the weight ratio of fenofibrate/hydrophilic polymer is between 1/10 and 4/1.

**Lacy *et al.* ('856)** teach carrier drug delivery systems for hydrophobic drugs and pharmaceutical compositions based thereon, which carrier comprises a digestible oil and a pharmaceutically acceptable surfactant component for dispersing the oil in vivo upon administration of the carrier, which comprises a hydrophilic surfactant, said surfactant component being such as not to substantially inhibit the in vivo lypolysis of the digestible oil

(see Abstract); (column 3, lines 38-67). The compositions are aimed at improving the bioavailability of hydrophobic drugs (col. 1, lines 4-7); (col. 2, lines 43-48).

Hydrophobic drugs which can be employed in the oral carrier systems include lipid regulating agents, such as fenofibrate (col. 12, lines 22-23); (col. 19, lines 45-50); and Example 6 at col. 21. The concentration of the drug lies in the range of 0.1% to 50% by weight (col. 12, lines 44-53). This range meets Applicant's claimed range of from 10 to 25% fenofibrate of instant claim 5.

Lacy teach that the hydrophobic drugs will reside predominantly within the dispersed (i.e., oil) phase of the emulsion as either a solution or partial suspension, as part of the biochemical and physical-chemical changes that occur with the drug formulation during passage of the gastrointestinal tract (col. 12, lines 63-67).

Lacy teach the inclusion of anionic surfactants, such as sodium lauryl sulphate (col. 7, lines 47-51). Hydrophilic surfactants can be provided in amounts of 10-60%. Lipophilic surfactants can be provided in amounts of 5-60% (col. 10, lines 20-29). Moreover, with regards to amounts and/or ranges, the Examiner points out that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

The pharmaceutical compositions for oral administration may be solid, liquid or semi-solid at ambient temperatures, but preferably are presented as liquids. Particularly preferred

compositions are liquid oral unit dosage forms, including those filled into hard or soft gelatin capsules (col. 14, lines 4-12).

Lacy does not teach inclusion of a hydrophilic polymer, such as polyvinylpyrrolidone (PVP).

**Curtet *et al.* ('726)** teach a fenofibrate composition comprising fenofibrate particles in combination with a solid surfactant and a hydrophilic polymer – polyvinylpyrrolidone (PVP), wherein the fenofibrate and solid surfactant have been co-micronized (see reference column 1, line 1 - col. 2, line 68); examples and claims. Curtet teach an intimate mixture of co-micronized fenofibrate and a solid surfactant, wherein the mixture is converted to granules in the presence of water (col. 2, lines 5-20). Curtet teach overlapping amounts of fenofibrate and the hydrophilic polymer- polyvinylpyrrolidone, wherein the fenofibrate is present in an amount of 200 mg per therapeutic unit (col. 1, lines 50-51) and the polyvinylpyrrolidone is contained in an amount of 7 mg (col. 3, lines 21-32). Surfactants, such as sodium lauryl-sulfate are disclosed in a recommended amount of between 0.5% and 7% by weight (col. 1, lines 52-60). Filling, dispersing and flow-enhancing excipients can be added and include lactose, starch, polyvinylpyrrolidone and magnesium stearate (col. 1, line 67 – col. 2, line 4).

The fenofibrate composition can be presented in the form of gelatin capsules, which are especially useful in the oral treatment of hyperlipidemia and hypercholesterolemia (col. 1, lines 44-49).

Curtet *et al.* teach that the weight ratio of surfactant/fenofibrate will be between about 0.75/100 and 10.5/100 (col. 1, lines 59-60). While the claimed weight ratio of the fenofibrate/hydrophilic polymer & claimed surfactant/hydrophilic polymer weight ratio is not

explicitly taught, it is the position of the Examiner that Applicants have not demonstrated any unexpected or superior results attributable to the claimed weight ratio of the fenofibrate/polymer & surfactant/polymer, nor the amounts of fenofibrate and polymer claimed. Suitable or effective weight ratios of drug/polymer, surfactant/polymer and amounts ranges of drug/polymer could be determined by one of ordinary skill in the pharmaceutical art through routine or manipulative experimentation to obtain optimal results, as these are indeed variable parameters attainable within the art.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a formulation of micronized fenofibrate comprising a hydrophilic polymer, such as PVP and a surfactant as taught by Curtet within the drug delivery carrier system of Lacy. One of ordinary skill in the art would be motivated to do so with a reasonable expectation of success because Curtet teach a fenofibrate composition comprising a combination of fenofibrate, PVP and a surfactant, which are employed to aid in increasing solubility and bioavailability of the active ingredient. The expected result would be an improved bioavailability fenofibrate formulation, for the effective treatment of hyperlipidemia and hypercholesterolemia.

* * * * *

**Claims 1-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lacy *et al.* (hereinafter "Lacy") (U.S. Pat. No. 5,645,856) in view of Santus *et al.* (hereinafter "Santus") (U.S. Pat. No. 5,460,828).**

The instant invention is drawn to a suspension of micronized fenofibrate in a solution of at least one hydrophilic polymer, wherein the weight ratio of fenofibrate/hydrophilic polymer is between 1/10 and 4/1.

**Lacy *et al.* ('856)** teach carrier drug delivery systems for hydrophobic drugs and pharmaceutical compositions based thereon, which carrier comprises a digestible oil and a pharmaceutically acceptable surfactant component for dispersing the oil in vivo upon administration of the carrier, which comprises a hydrophilic surfactant, said surfactant component being such as not to substantially inhibit the in vivo lypolysis of the digestible oil (see Abstract); (column 3, lines 38-67). The compositions are aimed at improving the bioavailability of hydrophobic drugs (col. 1, lines 4-7); (col. 2, lines 43-48).

Hydrophobic drugs which can be employed in the oral carrier systems include lipid regulating agents, such as fenofibrate (col. 12, lines 22-23); (col. 19, lines 45-50); and Example 6 at col. 21. The concentration of the drug lies in the range of 0.1% to 50% by weight (col. 12, lines 44-53). This range meets Applicant's claimed range of from 10 to 25% fenofibrate of instant claim 5.

Lacy teach that the hydrophobic drugs will reside predominantly within the dispersed (i.e., oil) phase of the emulsion as either a solution or partial suspension, as part of the biochemical and physical-chemical changes that occur with the drug formulation during passage of the gastrointestinal tract (col. 12, lines 63-67).

Lacy teach the inclusion of anionic surfactants, such as sodium lauryl sulphate (col. 7, lines 47-51). Hydrophilic surfactants can be provided in amounts of 10-60%. Lipophilic surfactants can be provided in amounts of 5-60% (col. 10, lines 20-29). Moreover, with regards to amounts

and/or ranges, the Examiner points out that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

The pharmaceutical compositions for oral administration may be solid, liquid or semi-solid at ambient temperatures, but preferably are presented as liquids. Particularly preferred compositions are liquid oral unit dosage forms, including those filled into hard or soft gelatin capsules (col. 14, lines 4-12).

Lacy does not teach inclusion of a hydrophilic polymer, such as polyvinylpyrrolidone (PVP).

**Santus *et al.* ('828)** teach a process for the preparation of microgranules suitable for suspension in fluids (see column 1, lines 1-35); (col. 3, lines 15-30). Active ingredients suitable for formulation into microgranules include lipid lowering drugs, such as fenofibrate (col. 5, line 6). Materials used for making the base granulate include binders, such as polyvinylpyrrolidone, polyvinylpyrrolidone/vinylacetate or any mixtures thereof (col. 5, lines 18-61).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a hydrophilic polymer, such as PVP as taught by Santus within the drug delivery carrier system of Lacy. One of ordinary skill in the art would be motivated to do so with a reasonable expectation of success because Santus teach microgranules that are suitable for use in liquid pharmaceutical compositions, such as suspensions, which comprise binders, particularly PVP, which is used as a suitable base material for the granulate for its' binding

properties. The expected result would be an improved fenofibrate formulation for the beneficial and effective treatment of hyperlipidemia and hypercholesterolemia.

* * * * *

**Claims 1-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Santus *et al.* (hereinafter "Santus") (U.S. Pat. No. 5,460,828) in view of Lacy *et al.* (hereinafter "Lacy") (U.S. Pat. No. 5,645,856).**

The instant invention is drawn to a suspension of micronized fenofibrate in a solution of at least one hydrophilic polymer, wherein the weight ratio of fenofibrate/hydrophilic polymer is between 1/10 and 4/1.

**Santus *et al.* ('828)** teach a process for the preparation of microgranules suitable for suspension in fluids (see column 1, lines 1-35); (col. 3, lines 15-30) and Abstract. Active ingredients suitable for formulation into microgranules include lipid lowering drugs, such as fenofibrate (col. 5, line 6). Materials used for making the base granulate include binders, such as polyvinylpyrrolidone, polyvinylpyrrolidone/vinylacetate or any mixtures thereof (col. 5, lines 18-61).

With regards to amounts and/or ranges claimed, the Examiner points out that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the

optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Santus does not teach the inclusion of a surfactant, such as sodium lauryl sulphate.

**Lacy *et al.* ('856)** teach carrier drug delivery systems for hydrophobic drugs and pharmaceutical compositions based thereon, which carrier comprises a digestible oil and a pharmaceutically acceptable surfactant component for dispersing the oil in vivo upon administration of the carrier, which comprises a hydrophilic surfactant, said surfactant component being such as not to substantially inhibit the in vivo lypolysis of the digestible oil (see Abstract); (column 3, lines 38-67). The compositions are aimed at improving the bioavailability of hydrophobic drugs (col. 1, lines 4-7); (col. 2, lines 43-48).

Lacy teach the inclusion of anionic surfactants, such as sodium lauryl sulphate (col. 7, lines 47-51). Hydrophilic surfactants can be provided in amounts of 10-60%. Lipophilic surfactants can be provided in amounts of 5-60% (col. 10, lines 20-29). The pharmaceutical compositions for oral administration may be solid, liquid or semi-solid at ambient temperatures, but preferably are presented as liquids. Particularly preferred compositions are liquid oral unit dosage forms, including those filled into hard or soft gelatin capsules (col. 14, lines 4-12).

Hydrophobic drugs which can be employed in the oral carrier systems include lipid regulating agents, such as fenofibrate (col. 12, lines 22-23); (col. 19, lines 45-50); and Example 6 at col. 21. The concentration of the drug lies in the range of 0.1% to 50% by weight (col. 12, lines 44-53).

Lacy teach that the hydrophobic drugs will reside predominantly within the dispersed (i.e., oil) phase of the emulsion as either a solution or partial suspension, as part of the biochemical and physical-chemical changes that occur with the drug formulation during passage of the gastrointestinal tract (col. 12, lines 63-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an anionic surfactant, such as sodium lauryl sulphate as taught by Lacy within the formulation of Santus. One of ordinary skill in the art would be motivated to do so with a reasonable expectation of success because Lacy teach drug delivery systems for hydrophobic drugs (i.e., fenofibrate) comprising surfactants, such as sodium lauryl sulphate, known for its' efficient wetting agent properties. The expected result would be an enhanced fenofibrate formulation for the therapeutically effective treatment of hyperlipidemia and hypercholesterolemia.

* * * * *

***Response to Arguments***

Applicant's arguments, see Response pages 2-5, filed 10/19/07, with respect to the rejection(s) of claim(s) 1-61 under 35 U.S.C. §103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Lacy *et al.* (USPN 5,645,856); Santus et al. (USPN 5,460,828) and Curtet *et al.* (USPN 4,895,726).

***Conclusion***

--No claims are allowed at this time.

**Correspondence**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday during regular business hours. (Wednesdays - Telework).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley, can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Humera N. Sheikh

HUMERA N SHEIKH
PRIMARY EXAMINER

Art Unit 1615

January 21, 2008

*hns*